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**INVITED REVIEW**

Male Endocrinology

# Testosterone and metabolic syndrome

**Glenn R Cunningham**

**Controversies surround the usefulness of identifying patients with the metabolic syndrome (MetS). Many of the components are accepted risk factors for cardiovascular disease (CVD). Although the MetS as defined includes many men with insulin resistance, insulin resistance is not universal. The low total testosterone (TT) and sex hormone binding globulin (SHBG) levels in these men are best explained by the hyperinsulinism and increased inflammatory cytokines that accompany obesity and increased waist circumference. It is informative that low SHBG levels predict future development of the MetS. Evidence is strong relating low TT levels to CVD in men with and without the MetS; however, the relationship may not be causal. The recommendations of the International Diabetes Federation for managing the MetS include cardiovascular risk assessment, lifestyle changes in diet, exercise, weight reduction and treatment of individual components of the MetS. Unfortunately, it is uncommon to see patients with the MetS lose and maintain a 10% weight loss. Recent reports showing testosterone treatment induced dramatic changes in weight, waist circumference, insulin sensitivity, hemoglobin A1c levels and improvements in each of the components of the MetS are intriguing. While some observational studies have reported that testosterone replacement therapy increases cardiovascular events, the Food and Drug Administration in the United States has reviewed these reports and found them to be seriously flawed. Large, randomized, placebo-controlled trials are needed to provide more definitive data regarding the efficacy and safety of this treatment in middle and older men with the MetS and low TT levels.**

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## INTRODUCTION

Some of the controversies that involve metabolic syndrome (MetS) and testosterone are: Do all men with the MetS have insulin resistance? Do low serum total testosterone (TT) levels cause the MetS? Should low TT be considered a cardiovascular risk factor? Is testosterone replacement therapy (TRT) an effective treatment for the MetS? Does TRT increase cardiovascular events?

This review will attempt to provide some background and current thinking regarding each of these questions. The relationship of low testosterone to MetS often is considered to be bidirectional; however, the relationships probably are not direct. The MetS is recognized as being associated with increased cardiovascular risk. Most clinicians consider low testosterone levels to be one cause of sexual dysfunction, and recent reports have associated low testosterone levels with increased cardiovascular mortality. Knowing how and when to evaluate cardiovascular risk is important for physicians who treat patients with low testosterone levels and/or erectile dysfunction. I will review some of the recent literature suggesting that TRT can cause weight loss, changes in body composition, improvements in insulin sensitivity and improvements in many of the components of the MetS. Finally, literature suggesting adverse cardiovascular effects of TRT will be addressed in this review.

## HISTORY AND DEFINITION OF METABOLIC SYNDROME

In 1998 Reaven presented his concept of Syndrome X at the Banting Lecture of the American Diabetes Association Annual Meeting.[1] He defined it as: (1) resistance to insulin-stimulated glucose uptake; (2) glucose intolerance; (3) hyperinsulinism; (4) increased very low density lipoprotein (triglycerides); (5) decreased high-density lipoprotein (HDL) cholesterol; (6) hypertension.

The National Cholesterol Education Program under the auspices of the National Heart, Lung and Blood Institute published the Adult Treatment Panel (ATP) III Clinical Identification of the MetS in 2001 (**Table 1**) (http://www.nhlbi.nih.gov/files/docs/guidelines/atp3xsum.pdf). These criteria were developed by an expert panel on detection, evaluation and treatment of high blood cholesterol in adults, and they have become widely accepted for identification of the MetS. While some have emphasized our lack of understanding of the cause for this grouping of clinical findings, this definition of MetS has made clinicians and patients more aware of these problems. However, the components usually are treated individually.

To better understand the similarities and differences between Syndrome X and the MetS, Cheal *et al*.[2] evaluated 443 healthy, nondiabetic volunteers with measurements of body mass index (BMI), blood pressure, fasting plasma glucose, triglycerides and HDL cholesterol. They also evaluated insulin resistance by infusing octreotide to suppress insulin secretion, insulin (32 mU $m^{-2}$ $min^{-1}$) and glucose (267 mg $m^{-2}$ $min^{-1}$). They drew blood at 10 min intervals between 150 and 180 min of the infusions to measure glucose and insulin concentrations. The averages of these four values were used to define the steady-state plasma glucose (SSPG) and insulin (SSPI) concentrations. Because SSPI concentrations were similar in all subjects, the SSPG concentration provided a direct measure of the ability of insulin to mediate glucose disposal. They defined insulin

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resistance as the top tertile of SSPG concentrations. Using the ATP III criteria to define MetS, 76% of these individuals were insulin resistant. However, the ATP III criteria only detected 46% of the subjects who were insulin resistant. Thus, the criteria were not very sensitive for detecting insulin resistance. Of the individuals who did not meet the ATP III criteria for having the MetS, 93% were insulin sensitive. When MetS was defined in this manner, it was associated with increased risk of cardiovascular events. The correlation coefficients of specific components of the MetS with SSPG ranged from 0.35 for fasting glucose to 0.50 for triglycerides.

The International Diabetes Federation (IDF) issued a consensus statement in 2013 in which they further defined MetS and the criteria for different races and ethnic groups (**Table 2**) (http://www.idf.org/metabolic syndrome). While central obesity and insulin resistance are thought to be very important, they state that the cause of the MetS is unclear. Genetics, physical inactivity, aging, a pro-inflammatory state and hormonal changes may have causal effects, but the role of each may vary depending on ethnicity. They concluded that waist circumference is more indicative of the MetS profile than BMI.

The IDF recognized that the upper limits of normal waist circumference varies between men (90 cm) and women (80 cm), and they accepted a waist circumference of > 94 cm for men of European descent. They also recognized that the ATP values (102 cm for men and 88 cm for females) are likely to continue to be used in the USA.

The IDF estimated that 20%–25% of the World's adult population have the MetS, and that having the MetS increases the risk of myocardial infarction or cerebrovascular accident three-fold and of death two-fold. The MetS is estimated to increase the risk of type 2 diabetes five-fold.

**Table 1: ATP III clinical identification of the metabolic syndrome (http://www.nhlbi.nih.gov/files/docs/guidelines/atp3xsum.pdf)**

| *Parameters* | *Measurement* |
|---|---|
| Waist circumference | |
| Male | >102 cm (>40 in) |
| Female | >88 cm (>35 in) |
| Triglycerides | ≥150 mg dl$^{-1}$ |
| HDL cholesterol | |
| Male | <40 mg dl$^{-1}$ |
| Female | <50 mg dl$^{-1}$ |
| BP | ≥130/≥85 mmHg |
| Fasting glucose | ≥110 mg dl$^{-1}$ |

Source: National Heart, Lung, and Blood Institute; National Institutes of Health; US Department of Health and Human Services. ATP: adult treatment panel; HDL: high density lipoprotein; BP: blood pressure

**Table 2: International diabetes federation criteria for diagnosis of metabolic syndrome (http://www.idf.org/metabolic syndrome)**

| *Central obesity (defined as waist circumference* with ethnicity specific values) plus any two of the following four factors* | |
|---|---|
| Raised triglycerides | ≥150 mg dl$^{-1}$ or<br>Specific treatment for this lipid abnormality |
| Reduced HDL cholesterol | <40 mg dl$^{-1}$ in males <50 mg dl$^{-1}$ in females or<br>Specific treatment for this lipid abnormality |
| Raised BP | Systolic BP ≥130 or diastolic BP ≥85 mmHg or<br>Treatment of previously diagnosed HTN |
| Raised FPG | FPG ≥100 mg dl$^{-1}$ or<br>Previously diagnosed type 2 DM<br>If above 100 mg dl$^{-1}$, OGTT is strongly recommended but is not necessary to define presence of the syndrome |

Source: International Diabetes Federation. HDL: high density lipoprotein; BP: blood pressure; HTN: hypertension; FPG: fasting plasma glucose; DM: diabetes mellitus; OGTT: oral glucose tolerance test; *see text

They also noted that cardiovascular mortality increases when more components of the syndrome are present.

## DETERMINATION OF CARDIOVASCULAR RISK

Many of the components of the MetS are recognized risk factors for the development of cardiovascular disease (CVD). A risk assessment calculator that uses information from the Framingham Heart Study was developed to predict a person's chance of having a heart attack in the next 10 years (http://cvdrisk.nhlbi.nih.gov/calculator.asp). This tool is designed for adults aged 20 and older who do not have heart disease or diabetes. This risk calculator utilizes age, gender, total cholesterol, HDL cholesterol, smoking status, systolic blood pressure and current use of anti-hypertensive medication. Individuals with low risk have 10% or less, intermediate risk 10%–20%, and high risk 20% or more risk of having a heart attack in 10 years.

In 2013, the American Heart Association and the American College of Cardiology introduced a new ASCVD risk estimator (http://tools.cardiosource.org/ASCVD-Risk-Estimator). The risk calculator estimates the 10-year and lifetime risk of having a coronary death, nonfatal myocardial infarct, fatal or nonfatal stroke. This estimator includes race and diabetes in addition to the components of the Framingham Risk Calculator. The 10-year risk is only calculated for individuals 40 to 79 years of age, and the lifetime risk is only calculated for individuals 20–59 years of age. Men and women with < 7.5% 10-year risk of a cardiovascular event are considered to be at low risk.

## ARE LOW T AND LOW SEX HORMONE BINDING GLOBULIN LEVELS ASSOCIATED WITH METABOLIC SYNDROME?

Multiple cross-sectional studies have found low TT and low sex hormone binding globulin (SHBG) levels in Caucasian and African-American men with the MetS, irrespective of age.[3–6] Low TT and SHBG levels also are prevalent in Chinese[7,8] and Korean[9] men with the MetS. Normally 40%–50% of TT is bound to SHBG, so reducing SHBG levels will decrease TT.

The association of low TT and low SHBG may be due to the hyperinsulinism in patients with Met S. Obesity is associated with hyperinsulinism. Hyperinsulinism suppresses SHBG synthesis and secretion by the liver.[10] Additional evidence supporting the role of hyperinsulinism was observed when a significant increase in SHBG levels occurred after acutely lowering insulin levels in obese men by treatment with diazoxide for 1 week.[11]

Estradiol levels are increased in men with the MetS, and they are positively correlated with the number of abnormal components of the MetS.[12] Although it is known that estrogen will increase SHBG levels, apparently the hyperinsulinism associated with obesity has a greater effect on SHBG levels. Estradiol also can inhibit luteinizing hormone (LH) secretion.[13] Many overweight and obese men respond to the selective estrogen receptor modulator, clomiphene citrate, by increasing LH and testosterone secretion.[14]

Inflammatory cytokines are thought to have a direct effect on the pituitary to reduce LH secretion[15] and also a direct effect on Leydig cell secretion of testosterone.[16] Both of these effects will decrease TT and free testosterone levels.

## DO LOW T LEVELS PREDICT DEVELOPMENT OF THE METABOLIC SYNDROME AND TYPE 2 DIABETES MELLITUS?

Low TT Levels have been shown to predict development of the MetS in men with normal BMI.[6,17,18] Laaksonen *et al.*[18] evaluated 702 men initially without the MetS or diabetes mellitus (DM). Men in the lowest quartiles of serum TT, calculated free testosterone (cFT) and SHBG at baseline had the highest odds ratios for developing the MetS or DM

during the 11 years follow-up. A meta-analysis reported incident MetS hazard ratios per quartile were 1.25 (95% confidence interval [CI]: 1.16–1.36), 1.44 (95% CI: 1.30–1.60) and 1.14 (95% CI: 1.01–1.28) for TT, SHBG and FT, respectively.[6] More recently, investigators conducting population-based studies have reported that only SHBG is associated with future development of the MetS.[19,20] Additional evidence that low TT increases the risk of MetS comes from androgen deprivation treatment of prostate cancer.[21,22]

## SHOULD LOW TOTAL TESTOSTERONE BE CONSIDERED A CARDIOVASCULAR RISK FACTOR?

Low TT and low bioavailable testosterone (bT) were each significantly associated with elevated 20 years risk of CVD mortality in an older population in which cause-specific mortality was age, adiposity, and lifestyle-adjusted.[23] The association of low TT with all cause and CVD mortality remained significant after excluding deaths that occurred during the first 5 years of follow-up. Phase 1 (1988–1991) data from the Third National Health and Nutrition Examination Survey III found the combination of low bT and ATP III-defined MetS is associated with increased cardiovascular mortality in men aged 40 years and above.[24]

A meta-analysis of the relationship between TT and CVD in healthy men[25] found an estimated relative risk of 1.01 (0.95 to 1.08) for studies of men younger than 70 years of age, and 0.84 (0.76 to 0.92) for studies of men over 70 years of age. Results were largely confirmed by separate analyses of free T and bT. They concluded that in elderly men, testosterone may weakly protect against CVD. Alternatively, low TT may indicate poor general health. A second meta-analysis found a relationship, but cautioned that it does not mean that low TT is causally related to mortality.[26] Muraleedharan and Jones[27] concluded that there is convincing evidence that low T is a biomarker for disease severity and mortality.

## TREATMENT OF THE METABOLIC SYNDROME

Recommendations from the 2013 Consensus Conference held by the IDF for management of the MetS include (http://www.idf.org/metabolic syndrome): (1) patients should undergo a full cardiovascular risk assessment (including smoking status) in conjunction with the following: moderate calorie restriction (to achieve a 5%–10% loss of body weight in the first year), moderate increase in physical activity, change in dietary composition. (2) If the lifestyle change is not enough and individual is considered to be at high risk for CVD, drug therapy may be required. (3) There is a need for a treatment that could modulate the underlying mechanisms of the MetS as a whole. (4) Treat the individual components of the syndrome.

## DOES TESTOSTERONE REPLACEMENT THERAPY IMPROVE COMPONENTS OF THE METABOLIC SYNDROME AND REDUCE MORTALITY?

### *Effects of testosterone replacement therapy on glucose metabolism*

The evidence that TRT improves insulin sensitivity and glucose control is conflicted. Marin *et al*.[28] were the first to report that testosterone improved insulin sensitivity assessed by euglycemic clamp studies in obese men while reducing central adiposity. A randomized, single center, double-blind, crossover trial demonstrated significant reduction in insulin resistance in hypogonadal men with type 2 diabetes.[29] These investigators subsequently participated in a multicenter placebo-controlled trial, called "the Times 2 Trial." In that study TRT decreased homeostasis model assessment of insulin resistance (HOMA-IR), but did not decrease A1c levels.[30] Many of the men had MetS, but did not have diabetes, and some of the men with diabetes had baseline A1c levels < 7%. A multi-center study involving seven general practices in the United Kingdom enrolled 211 patients in a 30 weeks double-blind, placebo-controlled trial using injectable testosterone undecanoate.[31] They reported TRT decreased A1c levels and waist circumference. Thirty-two men with MetS, newly diagnosed type 2 diabetes and a plasma testosterone level < 12 nmol $l^{-1}$ (346 ng $dl^{-1}$) were randomized to 52 weeks of treatment with diet and exercise with or without transdermal testosterone (50 mg per day).[32] Addition of testosterone to supervised diet and exercise resulted in greater therapeutic improvement of glycemic control and reversed the MetS in 81% versus 31% of controls after 52 weeks. An 18 weeks clinical trial in which obese Australian men with MetS were treated with intramuscular testosterone undecanoate or placebo reported improvement in insulin sensitivity.[33] A recent meta-analysis identified only five randomized clinical trials with a total of 351 subjects who were treated for an average of 6.5 months.[34] The meta-analysis found that fasting plasma glucose levels decreased 1.1 mmol $l^{-1}$, (95% CI: −1.88, −0.31), fasting serum insulin levels decreased−2.73 mIU $l^{-1}$ (−3.62, −1.84), hemoglobin A1c (HbA1c) decreased−0.87% (−1.32%, −0.42%).

Several trials have failed to observe improvements in glucose metabolism. Failure to improve insulin resistance or glucose control was reported in a 40 weeks, single center, randomized, parallel, placebo-controlled trial involving 88 men. Subjects had type 2 diabetes and testosterone levels < 346 ng $dl^{-1}$ (12 nmol $l^{-1}$).[35] I also am aware of two unpublished, industry-sponsored trials (one with a testosterone gel [T-gel] and the other with a testosterone patch) that failed to observe significant changes in HOMA-IR or A1c (ClinicalTrials.gov Identifier: NCT00141492; http://clinicaltrials.gov/ct2/show/NCT00141492?term = androgel + and + diabetes and rank = 3). Entry criteria were compromised because of recruitment difficulties in both trials. The T-gel study enrolled 180 men. They were randomized to T-gel (93) and placebo-gel (87), and they were treated for 6 months. Testosterone levels at the end of the study were 497.1 ng $dl^{-1}$ in the T-gel group and 263.3 ng $dl^{-1}$ in the placebo group. None of these trials have addressed effects of TRT on mortality.

The registry of patients who were treated with injectable testosterone undecanoate included 156 obese, diabetic men with T deficiency, aged 61.17 ± 6.18 years.[36] Testosterone treatment for up to 6 years decreased waist circumference by 11.56 cm, weight declined by 17.49 kg (15.04%), fasting glucose declined from 7.06 ± 1.74 mmol $l^{-1}$ to 5.59 ± 0.94 mmol $l^{-1}$ (127 ± 31 mg $dl^{-1}$ to 101 ± 17 mg $dl^{-1}$, $P < 0.0001$) and HbA1c decreased from 8.08% to 6.14%, with a mean change of 1.93%. Systolic and diastolic blood pressure, lipid profiles including total cholesterol: HDL ratio, C-reactive protein (CRP), and liver enzymes all improved ($P < 0.0001$). While this is not a clinical trial, it does suggest potential benefits of testosterone treatment on metabolic parameters when weight loss is achieved, and it suggests that long-term treatment with testosterone may contribute to weight loss.

It is widely recognized that testosterone treatment can reduce fat mass and increase lean body mass; however, until recently most reports have not been associated with much weight loss.[37] Changes in body composition and weight loss are considered potential mechanisms by which testosterone treatment improves insulin sensitivity and glucose control in patients with diabetes. Effects on inflammatory cytokines[38] and changes in oxidative metabolism[39] also have been reported to improve glucose metabolism.

A study designed to assess effects of acute changes in testosterone levels on glucose metabolism was performed as a randomized, double-blind, placebo-controlled, crossover study in 12 healthy young males who were studied on four separate occasions.[38] The subjects

received a gonadotropin-releasing hormone agonist 1 month before 3 of 4 trial days to induce castrate levels of testosterone. On trial days, a gel designed to deliver either high or low physiological doses of testosterone or placebo was applied to the body. On a fourth trial day, participants served as their own eugonadal controls. Each study comprised a 5-h basal period and a 3-h hyperinsulinemic euglycemic clamp. Acute testosterone deficiency was associated with increased high molecular weight adiponectin levels ($P = 0.03$) and increased oxidative glucose disposal ($P = 0.03$), but not total glucose disposal ($P = 0.07$). Acute T administration suppressed adiponectin, but did not affect total glucose disposal.

***Effects of testosterone replacement therapy on metabolic syndrome***

Testosterone replacement therapy has been reported to improve some or all of the components of the MetS. A few studies have been controlled, but none of the long-term studies are randomized, placebo-controlled clinical trials. The long-term observational studies with injectable testosterone undecanoate were associated with significant weight loss, so much of the metabolic improvement is likely due to the weight loss.

One hundred and eighty-four men, aged 35–70, with the MetS and hypogonadism (baseline TT level < 12 nm $l^{-1}$ [346 ng $dl^{-1}$] or cFT level < 225 pm $l^{-1}$ [6.5 ng $dl^{-1}$]) participated in a randomized, placebo-controlled 30 weeks trial with injectable testosterone undecanoate ($n = 113$; 1000 mg IM) or placebo ($n = 71$).[40] There were significant decreases in weight, BMI and waist circumference in the injectable testosterone undecanoate versus placebo group. Testosterone treatment decreased levels of leptin and insulin, but there were no changes in serum glucose or lipids. Interleukin-1 beta, tumor necrosis factor-alpha and CRP decreased.

In another report 20 hypogonadal men (mean T = 241 ng $dl^{-1}$ [8.4 nmol $l^{-1}$]) with the MetS (mean age 58) were treated with testosterone undecanoate injections every 12 weeks for 60 months.[41] Twenty matched subjects in whom testosterone treatment was unacceptable or contraindicated served as controls. Testosterone treatment resulted in significant reductions in waist circumference (−9.6 ± 3.8 cm, $P < 0.0001$), body weight (−15 ± 2.8 kg, $P < 0.0001$), and glycosylated hemoglobin (−1.6 ± 0.5%, $P < 0.0001$), and improvements in insulin sensitivity (HOMA-I; −2.8 ± 0.6, $P < 0.0001$), lipid profile (total/HDL-cholesterol ratio−2.9 ± 1.5, $P < 0.0001$), systolic and diastolic blood pressure (−23 ± 10 and−16 ± 8 mmHg, $P < 0.0001$, respectively.

Two hundred sixty-one patients (mean age 59.5 ± 8.4 years) diagnosed with late-onset-hypogonadism and erectile dysfunction were treated with injectable testosterone undecanoate in a prospective, observational, and longitudinal registry study.[42] The authors reported decreased weight, waist circumference, blood pressure, glucose, HbA1c, triglycerides and LDL cholesterol over the 5 years study. HDL cholesterol was increased.

A registry of 255 men, aged between 33 and 69 years (mean 58.02 ± 6.30) with subnormal plasma total T levels (mean: 9.93 ± 1.38; range: 5.89–12.13 nmol $l^{-1}$ [286 ± 40; 170–350 ng $dl^{-1}$]) and the MetS.[43] All men received treatment with injectable testosterone undecanoate 1000 mg at baseline and 6 weeks and thereafter every 12 weeks for up to 60 months. Testosterone therapy restored physiological testosterone levels and resulted in reductions in total cholesterol (7.29 ± 1.03 to 4.87 ± 0.29 mmol $l^{-1}$ [282 ± 40 to 188 ± 11 mg $dl^{-1}$]), low-density lipoprotein cholesterol (4.24 ± 1.07 to 2.84 ± 0.92 mmol $l^{-1}$ [164 ± 41 to 110 ± 35 mg $dl^{-1}$]) and triglycerides (3.14 ± 0.58 to 2.16 ± 0.13 mmol $l^{-1}$ [276 ± 51 to 190 ± 11 mg $dl^{-1}$]) and increased HDL cholesterol levels (1.45 ± 0.46 mmol $l^{-1}$ to 1.52 ± 0.45 mmol $l^{-1}$ [56 ± 18 to 59 ± 18 mg $dl^{-1}$]) ($P < 0.0001$ for all). There also were marked reductions in systolic (from 153.55 ± 17.6 to 137.72 ± 10.9 mmHg ($P < 0.0001$) and diastolic (93.49 ± 11.32 to 79.59 ± 7.36 mmHg ($P < 0.0001$) blood pressure, blood glucose (5.74 ± 0.8 mmol $l^{-1}$ to 5.41 ± 0.8 mmol $l^{-1}$ (98 ± 2 to 103 ± 14 mg $dl^{-1}$), HbA1c (7.06 ± 1.54% to 6.16 ± 1.35%) and CRP (6.29 ± 7.96 U $l^{-1}$ to 1.03 ± 1.89 U $l^{-1}$) ($P < 0.0001$).

Men with and without the MetS were evaluated in a 1 year registry of patients treated with a testosterone gel (Testim).[44] Only patients with the MetS demonstrated significant decreases in waist circumference, fasting blood glucose levels, and blood pressure. Lowest TT quartile patients demonstrated significant decreases in waist circumference and fasting blood glucose. Neither HDL cholesterol nor triglyceride levels changed significantly in either patient population.

## DOES TESTOSTERONE REPLACEMENT THERAPY INCREASE CARDIOVASCULAR EVENTS?

Cardiovascular disease in middle and older age men is the most common cause of death in the United States and in most other countries. This both emphasizes the importance of CVD and makes it difficult to detect small changes in mortality. The TOM Trial was stopped because of increased cardiovascular events.[45] This trial in older frail men was not designed nor powered to assess the cardiovascular effects of testosterone treatment in a population with a high prevalence of CVD. Retrospective reports based upon electronic medical records have associated testosterone treatment with both increased and decreased cardiovascular events. Dosing and duration of treatment are problematic and cardiovascular events were not adjudicated in these reports. Corona *et al*. conducted a systematic review and meta-analysis assessing major adverse cardiovascular events in men treated with testosterone or placebo.[46] The odds ratio was 1.01 ([0.57; 1.77]; $P = 0.98$). The odds ratio also was similar and not significant when all cardiovascular events were considered. The Food and Drug Administration in the United States has concluded that the current evidence does not indicate significantly increased risk, but trial data is needed (http://www.citizen.org/documents/2184_FDA%20Denial%20of%20Petition_July%2016, %202014.pdf).

## SUMMARY

Some of the controversies surrounding the MetS and low TT levels are being answered by large population based studies. The recent reports of significant weight loss, improvements in the components of the MetS and insulin sensitivity with injectable testosterone undecanoate of men with low TT and MetS and/or type 2 DM should encourage larger, placebo-controlled clinical trials. It also will be necessary to conduct a large clinical trial to assess cardiovascular and prostate risks.

## COMPETING INTERESTS

Research support: AbbVie; Advisory Panel: Apricus, Besins, Clarus, Endo Pharma, Ferring, Lilly, Repros Therapeutics; Consultant: Clarus, Ferring, Purdue, Repros Therapeutics.

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